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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER

ART UNIT | PAPER NUMBER

8

DATE MAILED:

This is a communication from the examiner in charge of your application
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 11/4/92 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1, 4 and 5-28 are pending in the application.
   Of the above, claims 5-13, 17-28 are withdrawn from consideration.
2. ☑ Claims 2, 3 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1, 4, 14-16 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 9-89)

752427

Claims 2 and 3 have been cancelled. Claims 1, 4 and 14-16 are currently under consideration.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure. The specification remains objected to because no enablement is seen for the production of antibodies, either monoclonal or polyclonal, that react with the protein of the invention or fragments thereof but do not cross-react with PDGF. Applicants have argued that an example of an approach to producing antibodies is provide in the specification at page 9, lines 10-20. This argument has been fully considered but is not deemed persuasive. The cited portion of the specification hypothesizes that "not all antibodies to CTGF will also be reactive with PDGF." However, no demonstration is found in the specification as filed of the actual production of such antibodies. Applicants have presented no factual basis for their assertion that not all anti-CTGF antibodies will be cross reactive with PDGF (how do applicants know that the non-homologous regions will necessarily be epitopic?). Further, it may well require screening an undue number of antibodies in order to find one with the claimed characteristics, if such even exists. Applicants protestation that the methods of obtaining the claimed antibodies have been adequately described does not obviate the need to show a reasonable expectation of success at doing so without undue experimentation on the part of the ordinary artisan. As applicants have failed to show that even a single antibody exists which has the claimed characteristics, this showing has not been made.

Claims 14-16 remain rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 1, 4 and 14-16 remain rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims remain indefinite for failing to adequately specify the protein of the invention. Applicants have asserted that the amendments to Claim 1 obviates this rejection (however they have failed to similarly amend Claim 14). This argument has been fully considered but is not deemed persuasive; the amendment does not overcome the rejection. As amended, Claim 1 reads on any mitogenic, chemotactic protein. The citation of the name that applicants have chosen to designate the protein of the invention fails to limit the claimed matter. Proteins are routinely characterized by their perceived function (hence names such as Connective Tissue Growth Factor, Follicle Stimulating Hormone, etc.); often the same protein is "discovered" several times, and given several different names, based on the different ways in which each group initially characterized it. The name or means of discovery or initial characterization does not render the protein novel. Applicants are advised to consult the prior Office Action at pages 2-3 for guidance in appropriate means of identifying proteins in patent claims. The Examiner notes that the conditions for determining the molecular weights cited in Claim 4 are not disclosed, therefore the cited molecular weights have little meaning.

The term "fragments" renders Claim 1 indefinite. Said term can be interpreted as encompassing every possible subset of the CTGF protein from a dipeptide to a protein lacking only a single amino acid from the wild type. Applicants have failed to adequately specify that which they see as their invention. Applicants are further reminded in amending this claim, that (when a definite set of fragments is specified) there must be description and enablement of such in the specification as filed. Applicant's amendment to this claim in deleting "functional" has failed to resolve this issue.

The amendment to Claim 14 has failed to address the objections raised in the prior Office Action; the claim remains indefinite for failing to define "specifically bind"; this may encompass all anti-PDGF antibodies which cross react with CTGF. Applicants have argued that "one skilled in the art would recognized the term "specifically refers to antibodies immunoreactive with

CTGF, but not PDGF" (p.6, §2 of the amendment). This argument has been fully considered but is not deemed persuasive; in the given context, the term in question might have the meaning alleged by applicants, but could equally validly encompass PDGF-cross-reactive antibodies, which unlike a non-specific binding protein such as Protein A, can be said to be specifically reactive with an entire group of proteins. To argue that only the former definition applies is to read limitations of the specification into the claims, which is not proper; the claims must be read in the broadest possible light.

In regard to the objection to the use in Claim 14 of "fragments thereof", applicants have argued that "fragments thereof refers to any portion of CTGF polypeptide which contains an epitope which binds an antibody that identifies CTGF." This definition, which does not appear in the claim, nevertheless fails to adequately define the metes and bounds of that which applicant sees as the invention. Were such language to be introduced into the claim, it would be found to be non-enabled in scope, as well as indefinite.

The objection to the use of "functional fragments" in Claim 1 has been obviated by amendment.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject

matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1 and 4 remain rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Matsuoka et al., or alternatively Campochiaro et la., or alternatively Shimokado et al., all as cited in the previous Office Action at pages 4-5.

Applicants have argued that Matsuoka did not adequately purify the protein of the invention (p.7§3), and that the mitogenic and chemotactic activities in Matsuoka correlated only with the 16-17 kD peptide as shown in Figure 4. This argument has been fully considered but is not deemed persuasive. With respect to the former point, the Examiner deems the protein to have been substantially purified to the point that a molecular weight determination could be made. The protein is deemed to have been purified sufficiently to meet the limits of the claims; however, methods of protein purification are well known in the art, and it is deemed to have been obvious to further purify the proteins describe by Matsuoka for the purpose of further characterizing and using them for their properties of mitogenicity. With respect to the latter point, careful examination of Figure 4 of the Matsuoka paper reveals that parts B and C, which indicate mitogenic and chemotactic activity, respectively, do not distinguish between the 16-17 and 34-36 kD species. It is only part A of the Figure which makes such a distinction. Further examination of the figure reveals that mitogenic activity of the PDGF-related peptides peaked at

approximately 5 days, and chemotactic activity of same peaked at approximately 4 days, a period during which the higher molecular weight species was increasing in prevalence, while the lower molecular weight species was either plateaued or declining, depending upon one's interpretation of Figure 4A. Thus, it remains that the 34-36 kD species described by Matsuoka et al. appears to be the same as that of the current invention.

Applicants have argued that Campochiaro et al. identified a family of PDGF related proteins, and did not specifically relate the mitogenic and chemotactic activities to the 36-38 kD species. This argument has been fully considered but is not deemed persuasive. Based on the disclosure by Campochiaro et al. it would have been obvious to the person of ordinary skill in the art to purify the individually disclosed species for the purpose of determining which possessed the chemotactic and mitogenic properties. Applicants have presented no evidence to indicate that the 36-38 kD species described by Campochiaro et al. is not the same as that of the current invention. In the absence of evidence to the contrary, the 36-38 kD protein of Campochiaro is deemed to be the same as that of the current invention.

With respect to Shimkado et al. , applicants argue that "it is not possible to say that a secreted protein(s) found on a gel in a region corresponding to a molecular weight (of) 37-39 kD is one protein and that that protein is the CTGF of the present invention." This argument has been fully considered but is not deemed persuasive. A prima facie case has been established in the prior Office Action that the Shimokado, Campochiaro, and Matsuoka and their co-workers all identified the protein of the current invention prior to the invention thereof by applicants. Applicants have failed to present evidence to refute the case of prima facie anticipation/obviousness presented by the Examiner. Mere allegations of uncertainty, that one cannot say conclusively on the basis of the prior art disclosures that the proteins described therein are that of the current invention, are not sufficient to overcome a finding of anticipation or obviousness.

Applicants' citation of Amgen v. Chugai is not considered to be relevant to the current case. The current claims are not to an isolated gene, but to a protein which appears to have been previously isolated and disclosed in the art.

Claims 1 and 4 remain rejected under 35 U.S.C. § 102(a) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Ryseck et al.

Applicants allege that they submitted the CTGF sequence to Genbank on 7/17/90, and thus predate the Ryseck disclosure. This information should be properly submitted in the form of a declaration under 37 C.F.R. §1.131.

Claims 14-16 remain rejected under 35 U.S.C. § 103 as being unpatentable over Matsuoka et al., or alternatively Campochiaro et al., or alternatively Shimokado et al., or alternatively Ryseck et al., as cited in the previous Office Action at page 6.

Applicants have argued that "there would not have been any motivation to combine any of the above-cited references to produce antibodies, since they teach other PDGF-related proteins, not CTGF." This argument has been fully considered but is not deemed persuasive. As stated above in the rejections under 35 U.S.C. §102 (b) or (a) or 103, applicants have not adequately shown that the proteins disclosed in the cited prior art are not that of the current invention. The Examiner further notes that no references were combined in this rejection, merely cited in the alternative.

Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication should be directed to Lorraine Spector, Ph.D. at telephone number (703) 308-1793.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1, fax number (703)308-4227. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

ROBERT J. HILL, JR.
SUPERVISORY PATENT EXAMINER
GROUP 1800

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